be used only in patients with serious arrhythmias unresponsive to routine therapy.

Mexiletine

Mexiletine is a structural analog of lidocaine that, however, is effective given orally. The oral dose ranges from 100 to 400 mg every six to eight hours. For urgent therapy, the intravenous route may be considered, with 200 to 250 mg given over five minutes, followed by an infusion of 60 to 90 mg an hour. Mexiletine is effective in suppressing ventricular arrhythmias; its definite role in the control of these arrhythmias, however, is still not defined. Most of the side effects occur during the initial period of therapy and later disappear in most patients during maintenance therapy. These side effects are frequently of central nervous system origin, including tremor, nystagmus, diplopia, dizziness, dysarthria, paresthesia, ataxia and confusion. Gastrointestinal side effects are common and include nausea, vomiting and dyspepsia. Thrombocytopenia and the presence of antinuclear antibody rarely occur but have been reported in some cases. Side effects are more likely to occur at plasma concentrations of greater than 1.5 to 2 μg per ml, which is very close to the therapeutic level. Cardiovascular effects of mexiletine are infrequent and include hypotension, bradycardia and exacerbation of arrhythmias. Mexiletine is generally well tolerated, however.

Tocainide

Tocainide is another structural analog of lidocaine and is, like mexiletine, effective against ventricular arrhythmias when given orally. Both tocainide and mexiletine have relatively long half-lives (12 hours).

In a number of clinical studies, tocainide has decreased the frequency of ventricular premature depolarizations, with variable side effects on ventricular tachycardia. The precise role of tocainide and the clinical setting in which the drug may eventually be used is still not defined. It would appear that tocainide will exert its antiarrhythmic efficacy at plasma concentrations above 6 μg per ml. The oral dosage regimen for tocainide is usually 400 to 600 mg every eight hours. Tocainide is generally well tolerated. Side effects include central nervous system disorders such as tremor, headache, sweating, altered hearing, dizziness, nervousness, hot flashes, paresthesia, blurred vision or diplopia, anxiety and lightheadedness. Gastrointestinal complaints, however, are more common and include anorexia, vomiting, nausea, abdominal pain and constipation.

These three antiarrhythmic agents hold the potential for dramatically increasing a clinician's ability to control serious cardiac arrhythmias. However, with their use comes the additional problem of serious side effects that must be carefully monitored by the physician.

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Clinical Use of Portable Insulin Pumps

AN ARRAY OF evidence supports the view that diabetic complications are attributable to the metabolic derangements caused by elevated blood glucose levels. This concept has been translated to patient care—thus the increased emphasis on blood glucose control. Ideally, changes in blood glucose levels would automatically be sensed and insulin appropriately released into the portal circulation. This could be accomplished with pancreatic islet cell transplantation or by an implantable glucose-controlled ("closed loop") insulin infusion system, a so-called artificial pancreas. While research into these areas continues, the development of blood glucose self-monitoring and patient-controlled external medication infusion pumps permitted clinical trials and now general clinical use of "open-loop" continuous subcutaneous insulin infusion (CSII) systems.

These insulin infusion devices, which use only short-acting insulin, consist of a syringe or an insulin reservoir in conjunction with a battery-operated pump controlled by an electronic mechanism that is designed for a relatively continuous infusion rate of insulin, the basal rate. This basal rate is supplemented by an increase in the insulin infusion rate controlled manually by the patient at mealtimes, the meal bolus. Patients must regularly—at least three to four times a day—monitor capillary blood glucose responses to the insulin infusion to insure adequate insulin doses. The insulin is delivered through disposable plastic tubing and a subcutaneous needle or catheter that is taped in place for one or two days. The newer pumps have alarms for battery failure, overdelivery and high pressure in the outflow system. The larger and nonprogrammable early pumps have been largely replaced by smaller, often preprogrammable devices that are easily concealed and do not interfere with most daily activities. Multiple basal infusion rates can be used for changing activity levels, and meal bolus injections can be adjusted for variable size, quality and timing of meals. These features provide patients with more freedom in their daily lives.

A policy statement from the American Diabetes Association states the primary indication for CSII:

> Failure to achieve an acceptable level of diabetic control in certain type I diabetic subjects with unusual fluctuations in blood glucose levels, despite intensive efforts with proper diet and multiple injections of insulin in single or mixture form and high patient motivation and compliance.

These guidelines include patients who have hyperglycemia associated with elevated glycosylated hemoglobin or patients with frequent hypoglycemic episodes as a result of trying to maintain blood glucose control. Hyperglycemia during pregnancy has been shown to be a definite risk to the fetus, and CSII in this setting can be especially useful for preventing diabetic complications of pregnancy. Some patients with insulin allergies are sensitive to the protamine or

zinc in the insulin preparations. These problems can be eliminated or minimized by infusing short-acting crystalline zinc insulin or, if necessary, a zincfree sodium insulin. Diabetic patients without any of the above indications also have used CSII to obtain more freedom in their life-styles—less restriction in meal timing and easier changing of work shifts or travel. Most patients have an improved sense of well-being when using CSII and they prefer to continue to use it even if blood glucose control has not improved. Possibly this is the result of a psychological effect of being in charge of their disease (the internal locus of control).

Data from our University of California, Irvine, clinic shows no statistically significant improvement in hemoglobin A_{1c} levels during 98 patient-years of CSII use in 46 patients. The mean hemoglobin A_{1c} value for these patients, however, was only mildly elevated (8.4%) before pump therapy and was 8.1% during CSII use.

Three major complications of pump therapy are diabetic ketoacidosis, hypoglycemia and infections at the infusion site—all of which have been associated with mortality. Due to the use of short-acting insulin, ketoacidosis develops rapidly when the insulin infusion is interrupted by tubing occlusion, leakage or mechanical failure of the pump. The accumulation of insulin crystals appears to be the main cause of needle occlusions. Ketoacidosis may be severe before blood glucose levels rise significantly, and patients using CSII may present with "euglycemic" ketoacidosis—that is, severe ketonemia preceding the rise in blood glucose concentrations. Various studies have reported a 2 to 17.5 times increase in the rate of ketoacidosis associated with CSII use. In our clinic the ketoacidosis rate is high before CSII use (0.17 events per year) and remained unchanged after CSII use (0.2 events per year). Although less frequent in these patients, hypoglycemia has occurred due to pump "runaway" and inappropriate insulin dosage through patient or provider error. In our clinic, however, the frequency of serious hypoglycemic episodes (requiring a hospital visit), was reduced from 3.0 events per year before to 0.2 events per year during CSII use and 87% of patients reported a greater than 50% reduction or complete elimination of severe hypoglycemic episodes during CSII use. For patients with ineffective glucose counterregulation, we recommend CSII use but alter our lowest acceptable blood glucose concentrations upward to the 100 to 150 mg per dl range. This treatment has produced remarkable results as described above. Insulin preparations contain antibacterial agents, but the indwelling needle or subcutaneous catheter can be a conduit for local infections when left in one site too long.

Among the solutions to these problems are the use of buffered insulins, appropriate insulin dilutions and daily changing of the infusion set and subcutaneous site with antiseptic care during insertion to avoid occlusions and infections. Patients need detailed instructions and repeated rehearsals to ensure problem-solving ability. Providers who prescribe CSII use should be aware of the possible complications, and an experienced clinician should be available to patients at all times.

The expense of insulin pumps ($1,000 to $2,500 initial costs plus daily supplies) and the requirement for a high degree of patient knowledge, motivation and participation have limited CSII use. Despite these difficulties, an estimated 8,000 to 10,000 insulin pumps are in use in the United States today. It remains to be proved whether the original goal of preventing long-term diabetic complications in large patient populations through sustained normoglycemia can be realized with CSII any more effectively than with multiple subcutaneous insulin injections combined with self-monitoring of blood glucose levels. We view pump use as an alternative insulin administration method that is associated with some serious complications that must be thoroughly considered before being prescribed and used.

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Human T-Cell Leukemia Virus (HTLV)

A VIRAL CAUSE of malignant conditions in humans has long been suspected, although there has been a paucity of confirmatory evidence. Recently, however, an etiologic association has been made between a unique type C retrovirus called human T-cell leukemia virus (HTLV-I), or adult T-cell leukemia virus (ATLV), and an unusual tumor of mature T cells in humans called adult T-cell leukemia/lymphoma. Originally thought to occur only in geographic areas where the virus is endemic, such as southwestern Japan and the Caribbean, the leukemic process has now been identified in other parts of the world, including the southeastern United States, parts of Africa and South America. This suggests that the virus is more widespread than initially thought. The onset of adult T-cell leukemia/lymphoma may be indolent; recently it has been recognized that clinically well patients may have antibodies to HTLV-I for many years before the development of symptomatic disease. The usual presentation of adult T-cell leukemia/lymphoma is abrupt, however, and is characterized clinically by lymphadenopathy, hepatosplenomegaly, skin lesions that may be clinically and pathologically indistinguishable from those of mycosis fungoides, hypercalcemia, lytic bone lesions and interstitial pulmonary infiltrates due either to lymphomatous infiltrates or to opportunistic infections. Involvement of the central nervous system is not uncommon. Malignant cells are found in the peripheral blood of most patients at some time during their course. Treatment usually consists of combination chemotherapy, though responses are generally short-lived, with few patients surviving more than a year.

The malignant virus-infected cells found in the peripheral blood and tissues of patients with adult T-cell leuke-